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Revealing the quality of movement: A meta-analysis review to quantify the thresholds to pathological variability during standing and walking

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ABSTRACT

Neuromotor processes are inherently noisy, which results in variability during movement and fluctuations in motor control. Although controversial, low levels of variability are traditionally considered healthy, while increased levels are thought to be pathological. This systematic review and meta-analysis of the literature investigates the thresholds between healthy and pathological task variability.

After examining 13,195 publications, 109 studies were included. Results from over 3000 healthy subjects and 2775 patients revealed an overall positive effect size of pathology on variability of 0.59 for walking and 0.80 for sway. For the coefficient of variation of stride time (ST) and sway area (SA), upper thresholds of 2.6% and 265 mm^2 discriminated pathological from asymptomatic performance, while 1.1% and 62 mm^2 identified the lower thresholds for pathological variability. This window of healthy performance now provides science based evidence for the discrimination of both extremely low and extremely high levels of variability in the identification as well as standardised monitoring of functional status in neurological cases.

Contents

1. Introduction

The effective performance of daily activities is based on relatively simple movements such as standing or walking. However, these tasks require complex control mechanisms within the human sensory motor system (HSMS) that provide timing, coordination and balance, and which deteriorate after the 6th decade of life (Aagaard et al., 2010). This decline in neuromotor control is reflected in an increased likelihood to fall (Prudham and Evans, 1981; Tinetti et al., 1988; Wickham et al., 1989) and suffer associated injuries (Nutt et al., 2011; O'Loughlin et al., 1993), and is even more accentuated in a variety of neurological disorders such as Parkinson's disease, dystonia, and dementia (Malatesta et al., 2003). An improved understanding of the interactions between the functioning of the HSMS and fundamental neuromotor ability is therefore critical to foster healthy aging and independent living.

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Although subjective and simple observational measures such as gait speed and posture can provide easy-to-use and relevant tests for the evaluation of neuromotor status in clinical settings, the monitoring of more subtle cases of functional degeneration, including the early identification of HSMS pathology and assessment of treatment efficacy, clearly require increasingly sensitive metrics. Here, a growing body of evidence now indicates that the variability of movement patterns, including postural sway and gait variability, is capable of reflecting not only the status of the HSMS, but also the overall quality of motor function (Hausdorff, 2009; Lord et al., 2011). In postural sway, variability describes the non-constant or fluctuating behaviour of the centre of body mass about a target point. During gait, variability describes the variation in movement patterns between repetitive cycles (Stergiou et al., 2006). Indeed, variability is an integral characteristic of any motor task (Bartlett et al., 2007). In general, movement arises from the integration of a multitude of central and peripheral neuromuscular systems to receive, process, and transmit information in order to plan and execute suitable actions (Frenkel-Toledo et al., 2005; Dietz, 1992; Kurz et al., 2012; Dietz, 2003; Ivanenko et al., 2009). However, each of these neuromotor processes, including sensory perception, cortical processing, neural signalling, and motor-neuron firing, is inherently noisy (Faisal et al., 2008) which is thought to result in variability during movement patterns and fluctuations in motor control. Concomitantly, an increase in motor variability has been observed through ageing and neuromotor pathologies (Hamacher et al., 2011; Hausdorff et al., 1998). Together, these observations have driven the consensus of proportionality between variability and task performance, leading to the traditional perspective that low levels of variability are healthy, while increased levels of variability reflect degenerated performance and malfunctioning of the HSMS.

Contrary to these clinical opinions, recent evidence suggests that variability is not entirely the result of noisy information, and is not necessarily disadvantageous. In this context, deterministic processes have been identified within movement variability that are distinguishable from random noise (Russell and Haworth, 2014; Dingwell and Cusumano, 2000; Dingwell and Kang, 2007; Huisinga Jessie et al., 2012; Roerdink et al., 2006), thereby indicating that control mechanisms within the HSMS are able to partially govern movement variability (Dingwell and Cusumano, 2000; Dingwell and Kang, 2007). Furthermore, it has been shown that movement variability can be adapted flexibly by subjects depending on the goal of a motor task (Wilson et al., 2008; Pekny et al., 2015; Wu et al., 2014) (consider the case of a trained darts or snooker player) or during motor learning (Harbourne and Stergiou, 2003). This evidence has cast sufficient doubt on the consensus of proportionality between variability and task performance that a hypothesis of *optimal levels of variability* has been proposed. Unlike the traditional linear association, it seems reasonable that a "U" shaped association characterises the relationship between motor performance and variability (Stergiou et al., 2006). Here, extremely high levels of variability as well as excessively low levels of variability are considered disadvantageous for motor performance. From a theoretical standpoint, the optimal feedback control theory claims that the HSMS not only considers the successful execution of a motor task (i.e. less variability reflects improved function), but also takes into account the high energy cost required for neuromotor control (Todorov and Jordan, 2002). On a practical level, the additional supra-spinal inputs might explain why subjects carefully placing a coffee pot on the table exhibited higher internal musculoskeletal forces (reflecting higher levels of energy expenditure) than was required to lift it again (lower level of control) (Westerhoff et al., 2009). Thus, movement tasks are likely to be executed at an optimum between sufficient accuracy and minimal control costs, which poses the question of whether an *optimal window of variability* exists while undertaking normal activities of daily living such as walking and standing. A more comprehensive understanding of movement variability could therefore establish the subtle aspects of movement "error" as a functional biomarker for the early identification of pathology or for monitoring disease progression, as well as for evaluating therapy efficacy in different patient groups.

The biggest hurdle for uptake of movement variability as a biomarker in clinical settings is the lack of clear definitions for optimum task performance. Considering the lifetime spent in performing and mastering walking and standing, it is plausible that healthy subjects perform these every-day tasks within an optimal window of variability. Since strong evidence indicates that subjects with a malfunctioning HSMS (i.e. neurological patients) will perform at levels outside of this window, a systematic review and meta-analysis of the copious literature assessing movement variability, including clinical cohorts, should allow the boundaries between normal physiological and pathological variability during movement to be discovered.

2. Methods

2.1. Publication search and selection

Between May and July 2014 a systematic literature review was conducted with the aim to comprehensively identify studies in which measures of variability during standing or walking were collected in both a cohort of healthy elderly and a cohort of patients with a neurological pathology. In order to do so, a common search string was entered into four different databases (Fig. 1). The search string containing Boolean operators was constructed so that an AND-combination of terms specified the *task* (*e.g. walk**), *measure* (*e.g. variability*) and *cohort* (*e.g. Parkin**). Within these categories synonyms as well as specifications of additional pathological cohorts were combined using the OR operator. Additionally a NOT-condition was applied to exclude studies involving e.g. animals, genes, heart-rate etc. The search was additionally limited to original research articles published after the year 1980. The complete search string can be observed in the electronic supplementary material.

After removal of duplicates, the search revealed 13′195 publications potentially relevant for the study. Titles and abstracts were screened by two reviewers (NK & NS) independently and excluded according to predefined criteria that ensured appropriateness of the studies to our research question. Disagreement between reviewers was solved by consensus. After the first screening, the complete manuscripts of the remaining 633 publications were retrieved. Here, 52 articles could not be acquired despite attempts to contact the authors directly. Subsequently the methods section of all articles was screened by both reviewers independently and studies were excluded in a similar process. Of the remaining 141 publications, relevant information on the task performed, measurement technology, outcome parameters and cohort information was extracted. During this process, a further 25 publications were excluded (please see complete list of exclusions in the electronic supplementary material) due to duplication of the data (multiple publications), incomplete data presentation or lack of methodological details, resulting in a set of 109 studies that were included in the meta-analysis.

2.2. Meta-analysis

The aim of the meta-analysis was two-fold: firstly, to assess the effect of malfunctioning of the HSMS on movement variability, and secondly to determine threshold levels that define the boundaries of healthy movement variability to pathology. In order to achieve this, means and standard deviations (SD) of variabil-

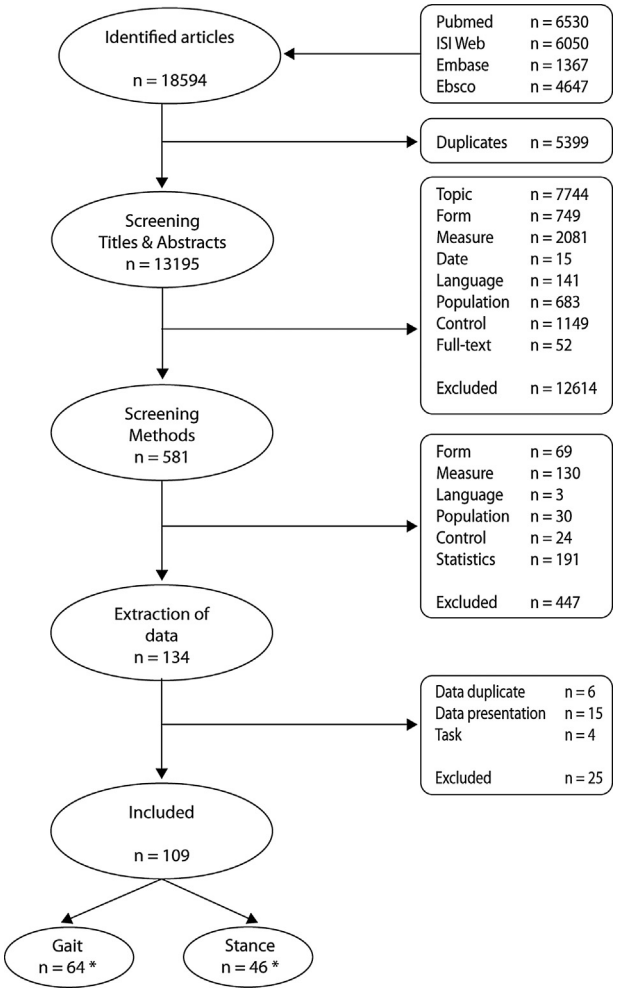

Fig. 1. PRISMA Flow diagram of publication screening and selection procedure. *Note that one study presented results on both walking and standing.

ity measures for both asymptomatic and neuromotor pathological cohorts were extracted. In cases where standard error of the mean (SEM) or 95% confidence intervals (95CI) were presented, these values were translated into SD as recommended by Cochrane. (Higgins and Green, 2011) An effect size (*ES*) for each study was then determined according to Cohen. (Cohen, 1988) In addition, each *ES* was corrected for sample size according to Eq. (1), adjusted to provide Hedges' g denoted as ES' (Lipsey and Wilson, 2001):

$$ES' = ES\left[1 - \frac{3}{4N-9}\right] \quad (1)$$

Finally, in order to assess the effect of a malfunctioning HSMS on variability during walking and standing, a mean *ES*' over all studies was calculated according to:

$$\overline{ES} = \frac{\sum(w \times ES)}{\sum w} \quad (2)$$

$$w = \frac{1}{se^2} \quad (3)$$

where w was a weighting factor determined using the standard error of measure, *se*. Heterogeneity was assessed using Cochrane's Q and I^2 statistics.

2.3. Statistical procedure for identification of thresholds for optimal variability

For each of the two tasks, walking and standing, a binary logistic regression (BLR) analysis was performed on the most commonly reported measures in order to assess how these parameters classify the two groups. The advantage of using BLR is that it provides an underlying continuous distribution (logistic curve-fit) of the dichotomous response variable (0 for healthy and 1 for pathological) in terms of the variability parameters. The logistic curve-fit was firstly analysed using the Chi-square goodness-of-fit test, while the quality of the classification was evaluated using a receiver-operating characteristic (ROC) procedure. For each of the commonly reported measures we then identified the optimal operating point, y_{fitoop} with balanced levels of sensitivity as well as specificity. This *optimal* y_{fitoop} according to Eq. (4):

$$\frac{log_e\left(\frac{y_{fitoop}}{1-y_{fitoop}} - b_0\right)}{b_1} = x_{oop} \quad (4)$$

was then used in an inverse binary logistic regression function in order to assess the optimal threshold value x_{oop} for each of the most commonly reported measures.

3. Results

3.1. Gait variability

The systematic search retrieved 64 publications reporting measures of variability during walking. In total this data was based on 1657 pathological (average mean age: 61.6 ± 15.2 years) and 1915 healthy control (average mean age: 59.7 ± 14.0 years) subjects, of which the majority of studies assessed patients with *basal ganglia disorders* (42 studies; 60%), comprising patients with Parkinson's or Huntington's disease. Mostly, subjects walked at self-selected speed over ground (56 studies; 81%) and gait patterns were assessed using footswitches (19 studies; 27%) or pressure sensitive carpets (18 studies; 26%). Approximately half of the studies (52%) included 50 or more steps in their analysis, which is reportedly required for reliable assessment of gait variability (Galna et al., 2013; Konig et al., 2014). The parameter most commonly reported was coefficient of variation of stride time (ST; 38 studies; 55%; Supplementary material; Table 1). The only parameters of gait to exhibit reduced variability in pathological cases were variability of step width (7 studies), and SD stance time (2 studies).

Within the 64 publications that were retrieved, multiple parameters as well as pathological groups were reported, resulting in a total of 119 *ES* values, with an I^2 value of 8.4%, and an average Cochrane's Q of 128.8. The forest plot (Fig. 2) reveals a positive effect size of pathology on variability with an *ES* = 0.59. All patient groups, except for the *Brain Injury* group showed a significantly increased variability during walking compared to the healthy group ($p < 0.01$; Table 1).

The BLR based on the parameter ST included a total of 38 studies with 739 pathological and 814 asymptomatic participants and revealed an area under the curve (AUC) of 0.8, a sensitivity of 0.8, and a specificity of 0.7. In the inverse logistic regression the corresponding optimal x_{oop} value was 2.6 [2.3;3.1]% ST. Only few studies reporting smaller values of ST for the pathological group were identified. Hence, the lower bound of physiological ST was estimated as the lowest observed group value for the asymptomatic subjects, which was 1.1% ST.

Table 1
Effect size statistics including the z-test and *p*-values across all patient groups for parameters of both gait variability and postural sway.

	Basal Ganglia Including: Parkinson's disease, Huntington's disease	Brain Injury Including: Stroke, Traumatic brain injury	Cerebellar Including: Cerebellar ataxia, Essential tremor, Spinocerebellar ataxia	Cognitive Including: Alzheimer's, Major affective disorders, Mild cognitive disorders, William's syndrome	Global Including: Multiple sclerosis, ALS, Progressive Supranuclear Palsy, Binswanger disease	Peripheral Including: Peripheral neuropathy	Overall
Gait parameters							
Mean effect size	0.60	0.41	1.11	0.46	0.41	1.29	0.59
Mean standard error	0.07	0.31	0.27	0.13	0.19	0.41	0.06
Number of comparisons	77	6	6	17	10	1	119
Cochrane's Q	59.6	11.4	3.6	23.8	18.1	3.6	129.1 (120.1 8.9)[a]
Z-test	8.25	1.30	4.09	3.58	2.16	3.16	10.25
p-value	<0.01	0.10	<0.01	<0.01	0.02	<0.01	<0.01
Sway parameters							
Mean effect size	0.63	0.81	1.16	2.21	0.87	0.99	0.80
Mean standard error	0.11	0.12	0.37	0.40	0.27	0.40	0.07
Number of comparisons	34	25	5	3	6	3	77
Cochrane's Q	48.7	18.3	19.9	11.3	0.9	7.0	121.7 (106.1 15.7)[a]
Z-test	5.73	6.58	3.12	5.47	3.22	2.50	10.80
p-Value	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

[a] The values for between and within group homogeneity statistics are included.

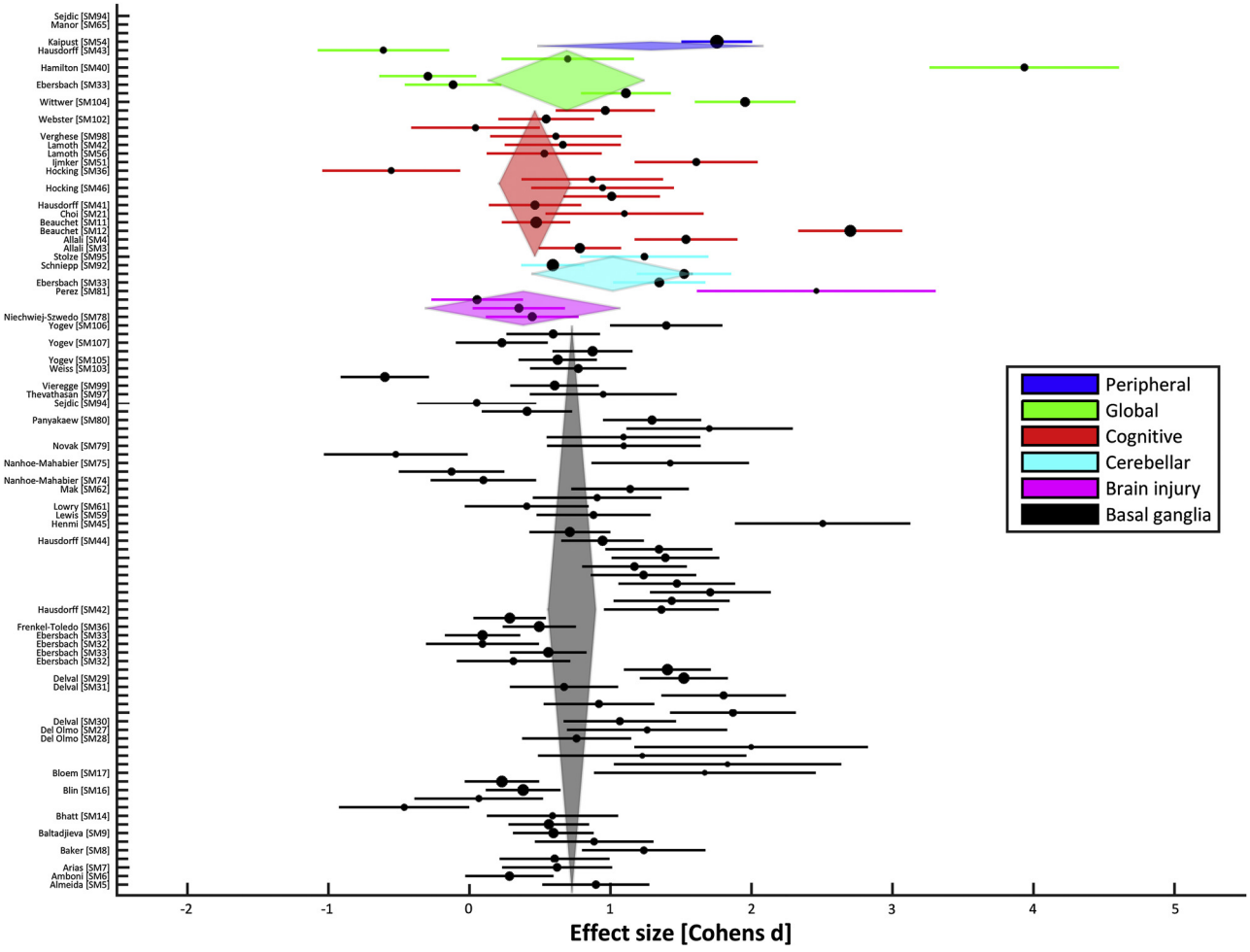

Fig. 2. Forest plot for gait parameters that presents the effect sizes for different neurological pathology groupings (see Table 1), but also the mean effect size of 0.59 based on 1657 pathological and 1915 healthy subjects (shown as a yellow diamond). Analysis of these results indicates that a CV of stride time of 2.6% discriminates healthy from pathological motor variability.

3.2. Postural sway

The systematic search for postural sway revealed 46 studies in total. This included a total of 1118 pathological subjects (average mean age: 59.4 ± 10.2 years) and 1086 healthy controls (average mean age: 58.8 ± 12.1 years). The majority of patients belonged to the *basal ganglia* (20 studies; 41%) or *brain injury* (16 studies; 33%) groups. Mostly, subjects were measured using force plates (40 studies; 83%) in an erect posture with their eyes open (44 studies; 91%). The parameter most commonly reported was sway area (SA; 26 studies; 54%; Supplementary Table 2). The majority of studies (89%) included standing trials of 30 seconds or longer, which has been defined as a prerequisite for the reliable assessment of sway (Pinsault and Vuillerme, 2009). All parameters of sway were increased in pathological cases except for sway in the anterior-posterior direction (1 study), and frequency of sway in the anterior-posterior direction (1 study).

Similar to gait variability, multiple parameters as well as pathological groups were reported, resulting in a total of 77 *ES* comparisons, with an I^2 value of 37.6%, and an average Cochrane's Q of 121.7. An overall positive effect of pathology on standing sway became apparent with a significant effect size of 0.8 ($p < 0.01$; Table 1). All patient groups showed significantly increased postural sway compared to healthy subjects ($p < 0.01$).

BLR based on the parameter SA included 26 studies with 447 patients and 420 asymptomatic participants, and revealed an AUC of 0.6, a sensitivity of 0.6, and a specificity of 0.7. Inverse regression revealed the higher bound of physiological SA to be x_{oop} =265.0 [149.7;480.0] mm^2. The lowest reported sway area among asymptomatic participants across all studies revealed the lower bound of physiological SA as 66.7 mm^2 (Fig. 3).

4. Discussion

Patients with neurological pathologies exhibit exaggerated movement and control patterns, but the limits between physiologically normal and pathological variability during walking and standing have remained elusive. This review and meta-analysis of over 13′000 scientific articles now provides the highest level of evidence to elucidate the relationship between functioning of the HSMS and motor task performance, and was therefore clearly indicated. For the most commonly reported parameters of ST and SA, an upper threshold level of 2.6% and 265.0 mm^2 discriminates pathological from asymptomatic performance with an overall accuracy of 80% and 60% for walking and standing respectively. Only a low number of studies have reported decreased variability for the pathological groups, restricting statistical conclusions. Interestingly, all patient groups exhibited increased postural sway, irrespective of whether they suffered from hypo- or hyperkinetic movement disorders. The lowest measured ST and SA in an asymptomatic cohort suggests that 1.1% and 62 mm^2 are reasonable boundaries for identifying pathological motor patterns. For the first

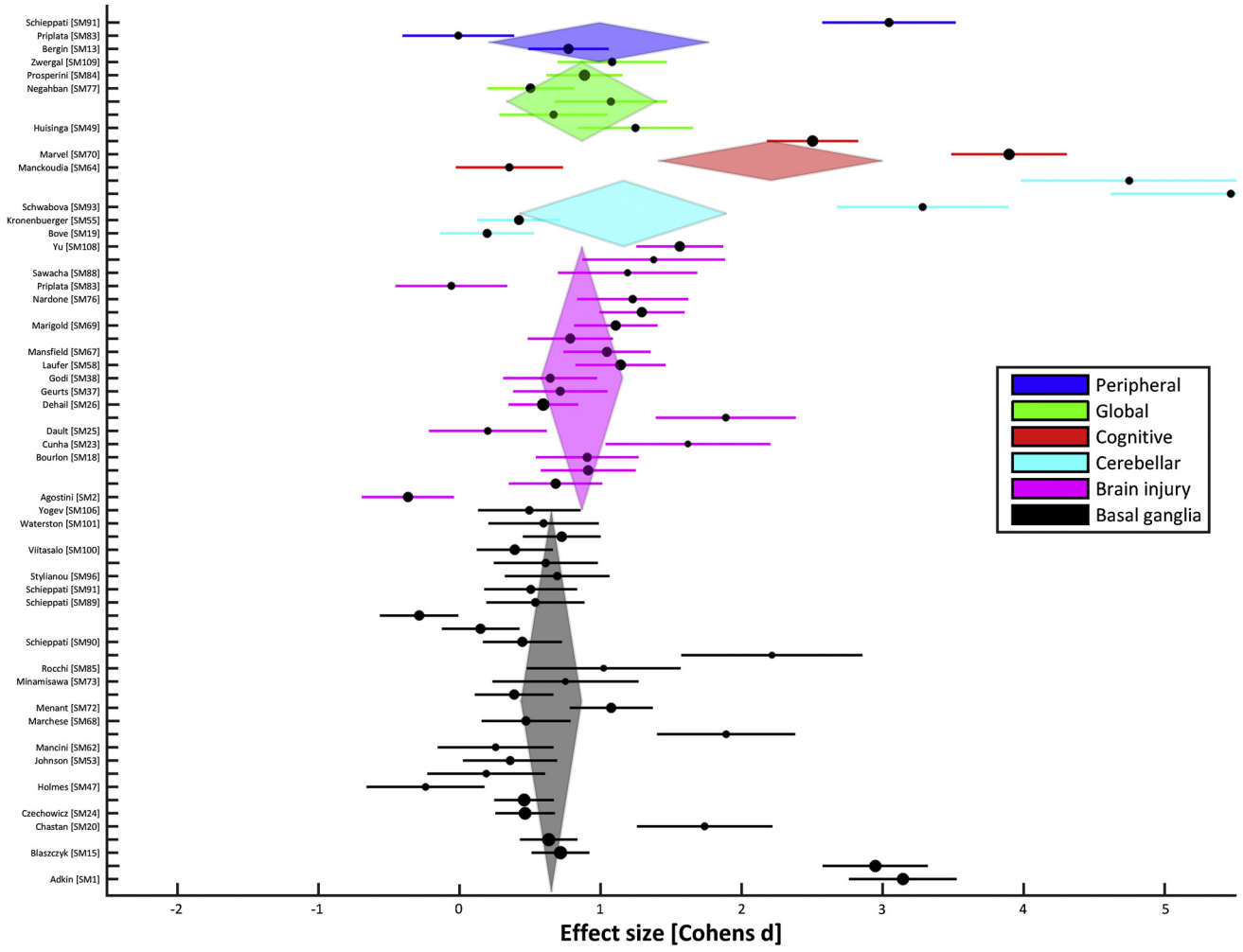

Fig. 3. Forest plot for sway parameters that presents the effect sizes for different neurological pathology groupings (see Table 1), and shows a mean effect size of 0.8 based on 1118 pathological and 1086 healthy subjects (shown as a yellow diamond). Analysis of these results indicates that a sway area of 265.0 mm^2 discriminates healthy from pathological sway.

time, these boundaries for physiological vs. pathological performance demonstrate the power of movement variability to serve as a functional biomarker for the identification of neuromotor pathologies, as well as a target for treatment outcome or for the modulation of therapy dosage in clinical practice.

Based on the presented data, it would appear that the current meta-analysis not only represents the effect of pathology on movement performance, but also the effect of disease severity. Further comparison of the clinical disease rating scales and the associated ESs revealed that lesser affected patient cohorts produced smaller ESs for stance[SM53, SM100, SM106] as well as for gait, where the UPDRS motor subscale scores were positively associated to ESs (Pearson correlation: $r = 0.44$; $p = 0.09$)[SM29, SM30, SM32, SM60, SM80, SM86, SM103, SM105, SM106&SM107]. Similarly, the stance of Parkinson's patients measured in the ON medication state (81% of studies; average ES = 0.6) produced a smaller ES compared to those tested in the OFF state (average ES = 1.0). However, no effect of the levodopa status was observed in the gait dataset (72% of studies measured walking in the ON condition). Here, average ESs for the two subgroups were similar with 0.54 and 0.58 for both the ON and OFF states respectively. We assume that this finding is due to biased patient selection, as studies measuring walking performance in the OFF condition might include less severely affected patients in order to successfully complete the measurement protocol.

As apparent from the almost consistent increase in variability across all investigated patient cohorts, it can be concluded that any disturbance within the HSMS leads to a more variable motor performance. However, a detailed examination of the data suggests that different parameters of gait and balance exhibit varying behaviour with pathology. In the gait dataset, particularly within the Basal ganglia group, it appears that stride time or stride length variability results in large positive *ESs*[e.g.SM44, SM32]. Conversely, negative *ESs* were almost exclusively observed for measures of step-width variability[e.g.SM14, SM86, SM99]. This observation might indicate that progressive decline in lower extremity muscle tone and postural reflexes in Parkinson patients could lead to reduced levels of variability of step width, primarily to maintain a stable centre of mass in the medio-lateral direction (Rochester et al., 2014). This result suggests that relaxing control of one dimension may allow control of another to be tightened, or vice versa, thus selectively heightening sensory feedback towards parameters that are critical for successful task performance (Todorov and Jordan, 2002). It is therefore reasonable that due to the *multidimensionality of variability*, different pathologies of the HSMS exhibit specific and subtle movement signatures or, alternatively, that movement signatures are the result of compensation mechanisms that make successful task performance possible, and that depend upon the disorder (Lord et al., 2013). Similarly, it has been shown that the cerebellar group shows largest ESs for measures that quantify consistency

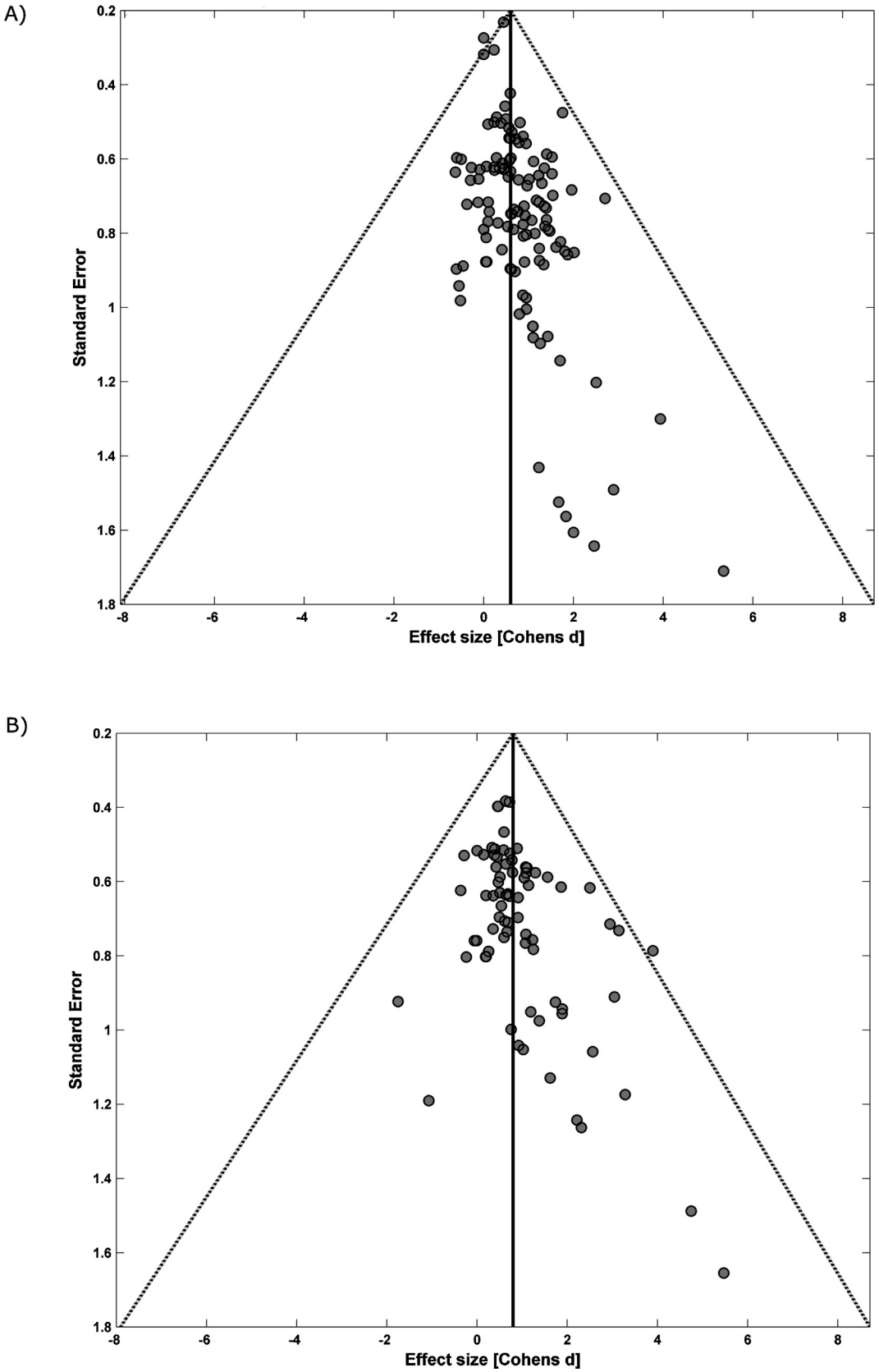

Fig. 4. Funnel plot for studies reporting on (A) gait task and (B) stance task.

of forward progression (e.g. step length variability)[SM33, SM35, SM92]. This result is in accordance with findings of Schniepp and colleagues who showed that spatio-temporal variability in patients with cerebellar ataxia is markedly increased compared to values of patients with Parkinson's disease, as well as those with supranuclear palsy (Pradhan et al., 2015). It is therefore plausible that the cerebellum plays a prominent role in controlling balance in the anterior-posterior direction, whereas rhythmicity of movement (represented by variability of stride time) is less affected in these patients[SM92]. The complex inter-dependency between the pathology of different neurophysiological structures and parameters of variability in the motor outcome therefore limits any clear interpretation of the cause-effect relationships.

This review has highlighted the similarity in motor outcome between subjects with a variety of neurological pathologies. However, to gain a full understanding of the inter-relationships between the specific neural pathology and their motor function, multivariate analyses that examine the subtle variations in movement signatures, including e.g. combinations of temporal and spatial, as well as non-linear measures of movement performance, are clearly indicated. It remains unclear whether an *optimal level of variability* for motor performance exists (Stergiou et al., 2006). From a traditional perspective, extremely high levels of variability have been considered detrimental, and have been associated with unstable task performance. However, extremely low levels of variability, although still largely elusive in the scientific literature, might indicate a functionally rigid system with only a limited capacity to adjust to internal and external perturbations. Recent empirical studies now suggest that subjects with a diminishing skill level (e.g. a positive history of falling) have either lower or higher levels of variability compared to their asymptomatic counterparts (Singh et al., 2012; Brach et al., 2005). However, these single reports have only provided limited evidence to support the hypothesis of a "U-shaped" relationship between variability and functional performance. In addition, a discussion on the appropriateness of magnitude measures of variability to represent unstable and rigid movement performance is clearly required. In addition, methods that are able to characterise the *structure* of variability throughout a time series may well provide additional validity or sensitivity to the analyses performed (Stergiou et al., 2006; Dingwell and Cusumano, 2000; Dingwell and Kang, 2007; Roerdink et al., 2006).

The logistic regression presented in this study of the literature has only considered the CV of stride time and sway area as the two most frequently reported gait and balance variables. Here, reliability of the presented data needs to be critically evaluated. In the case of studies that examined walking, only half fulfilled the requirements for reliable data collection, where it is suggested that at least 50 steps are necessary for the reliable assessment of gait variability (Galna et al., 2013; Konig et al., 2014). Interestingly however, a comparison of ESs between studies that included more than 50 steps compared against those with fewer showed no significant differences. This surprising outcome is possibly the result of the same low-reliability protocols being used to examine both the pathological and the control cohorts, thus affecting both groups equally.

Two possible limitations of this systematic review are likely to influence our understanding of the inter-relationships between motor variability and functional performance. Critically, publication bias, and the lack of reported unexpected or negative results, is a general problem that is difficult to overcome. It seems plausible that observations contradicting the general consensus about a malfunctioning HSMS resulting in increased levels of variability might be considered false, with reduced chances of successful publication. This potentially leads to overestimation of the mean ES found in the meta-analysis. Indeed, the funnel plots of our data (Fig. 4) show asymmetrical distribution towards positive ESs, which is indicative of reduced likelihood of studies being published that report negative or no ESs (i.e. a pathological cohort performs with lower levels of variability). However, asymmetry in the funnel plots was mainly caused by small studies with large standard errors. More trustworthy studies with smaller standard errors were also mostly equally distributed around the mean ES. As the mean ES was calculated based on each ES weighted by their standard error (Eqs. (2) & (3)) the risk of ES overestimation in this meta-analysis was minimised. In addition, most commonly applied statistical approaches assume a linear relationship or a one-sided difference between groups. However, under these conditions, a "U-shaped" association would remain uncovered due to misleading averaging of the data, resulting in inappropriate pooling into single datasets with high variance. The outcome is that only few differences between groups become apparent, possibly further increasing publication bias. Furthermore, studies that average extremely high with extremely low results would result in *ESs* close to zero, hence leading to an underestimation of the boundaries between physiological and pathological variability proposed here. In this respect, studies utilising more appropriate analyses that consider the position of each case within the population examined, should allow recognition of non-linear relationships between cohorts.

In this meta-analysis, it is important to consider the lack of detailed information on specific cases and their diagnosis, which might have led to inconsistent group allocation. For example, it is possible that the "brain injury" group could have included subjects with injuries to the basal ganglia. Unfortunately, as this information could not be corroborated during the review process, it was not possible to determine the uniformity of the allocations. However, it would appear that the choice of functional parameter (e.g. variation of stride time vs. variation of step width) rather than the underlying pathology is dominant in guiding the direction and magnitude of the ESs. In a similar manner, heterogeneity between publications is a crucial aspect in meta-analyses. For gait variability, an I^2 value of 8.4% was obtained, which represents excellent consistency between studies. Although the studies that considered sway revealed a higher I^2 value of 37.6%, this is still within the recommended guidelines (Higgins and Green, 2011). Considering the large variety in populations, study assessment techniques, protocols, age of cohorts, sample sizes etc., I^2 values of between 8.4% and 37.6% could still be considered very good.

In conclusion, despite possible influence of publication bias, the data reviewed in this study suggest that any disturbance of the HSMS is likely to result in an increase in movement variability. Reduced levels of variability are only present for a few parameters of walking and standing, and thus pose the question of the neural aetiology in such cases. Based on the theoretical consideration of excessively low levels of variability, we therefore suggest that individual performance comparisons be presented in addition to group-based statistics. However, based on the results of over 3000 healthy subjects and 2775 patients, this meta-analysis indicates that a CV of stride time between 1.1% and 2.6%, and a sway area of between 67 mm^2 and 265 mm^2 indicate healthy neuromotor function. These values can now be used in clinical settings for identification of subtle changes while monitoring motor performance.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2016.03.035.

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